REMARKS

Claims 6-21 are pending in the present application and Claims 15 and 17 have been amended herein. Applicants will address each of the rejections of Claims 6-21 in the order in which they appear in the Office Action dated June 7, 2004.

Rejection of Claims 15 and 16 under 35 U.S.C. § 112, First Paragraph

Claims 15 and 16 have been rejected under 35 U.S.C. § 112, first paragraph, for their inclusion of the prevention of arthritis in the claimed method. Though Applicants respectfully disagree with the basis for this rejection, they have by amendment herein deleted "or preventing" from Claim 15 to expedite prosecution of the present application. Applicants retain their right to file a divisional patent application claiming the methods of prevention in the present application.

In view of this amendment, Applicants respectfully ask that this rejection of Claims 15 and 16 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejection of Claims 15 and 16 under 35 U.S.C. § 102(e)

Claims 15 and 16 are rejected under 35 U.S.C. § 102(e) for their inclusion of the prevention of arthritis in the claimed method. Though Applicants disagree with the basis for this rejection, "or preventing" has been deleted from Claim 15, as noted above. Applicants retain their right to file a divisional patent application claiming the methods of prevention in the present application.

In view of this amendment, Applicants respectfully ask that this rejection of Claims 15 and 16 under 35 U.S.C. § 102(e) be withdrawn.

Rejection of Claims 6-21 under 35 U.S.C. § 103(a)

Claims 6-21 have been rejected under 35 U.S.C. § 103(a) over Sherle et al. (The Journal of Immunology, 1998 Oct; 161: 5681-5686) and McGilvray et al. (The Journal of Biological Chemistry, 1997; 272(15): 10287-10294), in view of Bridges (WO 98/37881). Applicants

respectfully disagree with the basis for this rejection and wish to reiterate the arguments concerning the McGilvray et al. reference in Applicants' response dated September 22, 2003. Simply demonstrating reduced monocyte activity with a MEK inhibitor following one specific stimulus and assessing less relevant endpoints, such as described by McGilvray et al., would not lead one of skill in the art to consider arthritis as an indication for treatment.

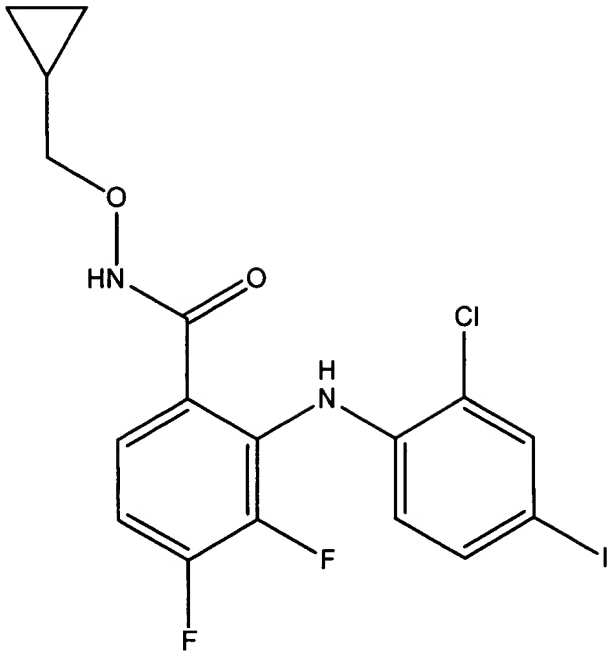
In addition, the teachings of Scherle et al. and McGilvray et al. concerning the MEK inhibitors U0126 and PD98059 do not suggest the unexpected improvements in MEK inhibition and more desirable pharmaceutical qualities of the compounds of the presently claimed methods of treatment. As evidence of these unexpected qualities, Applicants enclose the following articles:

1. *Specificity and mechanism of action of some commonly used protein kinase inhibitors*, Davies et al., Biochem. J. (2000) 351, 95-105;

2. *Cell-cycle arrest by PD184352 requires inhibition of Extracellular signal-regulated kinases (ERK) 1/2 but not ERK5/BMK1*, Squires et al., Biochem. J. (2002) 366, 673-680; and

3. *MEK Inhibitors: A Therapeutic Approach to Targeting the Ras-MAP Kinase Pathway in Tumors*, Sebolt-Leopold, Current Pharmaceutical Design, 2004, 10, 1907-1914.

Davies et al. (Biochem. J. (2000) 351, 95-105) discusses the protein kinase inhibiting abilities of a number of compounds, including U0126, PD98059 and PD184352, which is the compound seen at page 23, lines 10-11, and in Claim 13 at page 102, lines 30 and 31 of the present application. PD184352 has the structure and name shown below.



PD-184532

2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide

In Table 1 on page 98, Davies et al. list the MKK1 protein kinase activity as a percentage of control following treatment with a 10 μM concentration of U0126 (56±1), PD184352 (5±1) and PD98059 (89±1). Nothing in the cited Scherle et al. and McGilvray et al. references suggest the significant and pharmaceutically desirable improvement in MKK1 inhibitory activity demonstrated by PD184352 over that of U0126 and PD98059.

Squires et al. discuss the improved selectivity of PD184352 over that of U0126 and PD98059. In their abstract, Squires et al. state that PD98059 and U0126 inhibit the ERK1/2 (MEK1/2) pathway, but also inhibit the ERK5/BMK1 pathway. Squires et al. then state "serum-stimulated ERK1 activity was completely inhibited by PD184352 with and IC_{50} below 1 μM, whereas ERK5 activation was unaffected even at 20 μM."

In her article, Judith Sebolt-Leopold discusses the undesirable pharmaceutical nature of PD98059 and U0126 and the merits of PD184352. At page 1909, second column, third full paragraph, she states:

> "PD98059 (Fig. 2) represents the first MEK inhibitor identified in an *in vitro* screen for inhibitors of ERK activation [54, 55]. Because of its pharmaceutical limitations, including insolubility, this compound was released to the academic community ..."

Similarly, Dr. Sebolt-Leopold writes in the first column of page 1910 that U0126 "was not pursued clinically, presumably due to its reported lack of *in vivo* activity".

In the third paragraph in the left column of page 1910, Dr. Sebolt-Leopold notes that PD184352 provided much needed in vivo validation for targeting MEK and:

> "Importantly, efficacy was achieved at well-tolerated doses and correlated with a reduction in the levels of activated ERK in excised tumors [60]. As will be discussed shortly, this agent was advanced into clinical oncology trials...".

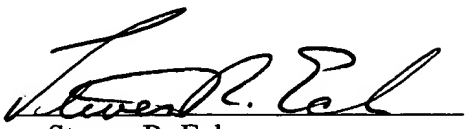
Nothing in the Scherle et al. and McGilvray et al. references teaches or suggests these unexpected merits of PD194352 in in vitro administrations and over those of U0126 and PD98059, each of which is desirable for pharmaceutical administration and particularly relevant to the presently claimed methods of treatment.

In view of the foregoing Applicants respectfully ask for reconsideration and withdrawal of the rejection of Claims 6-21 under 35 U.S.C. § 103(a).

In view of the amendments and remarks herein, Applicants respectfully submit the present application is now in condition for allowance. A decision to that effect is respectfully solicited.

The Commissioner is authorized to charge any fee or credit any over payment in connection with this communication to our Deposit Account No. 23-0455.

Respectfully submitted,

By: 

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Enclosures: Biochem. J. (2000) 351, 95-105
Biochem. J. (2002) 366, 673-680
Current Pharmaceutical Design, 2004, 10, 1907-1914